

Clinical Investigations of the Potential Effects of Anesthetics on Pediatric Neurological Development

Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research, FDA

DISCLAIMER

- This presentation is limited to information that is currently in the public domain.
- FDA has not reviewed either the protocols for or the data generated by these studies.
- This presentation is to help focus the clinical discussion, not to critique the work done to date.

Clinical Investigations

- Retrospective Epidemiological Studies
 - Denmark
 - Netherlands
 - Mayo Clinic
 - New York State
 - Australia
- Prospective Epidemiological Study
 - PANDA Study
- Prospective Randomized Controlled Study
 - General Anesthesia/Spinal (GAS) Study
 - Mayo Anesthesia Safety in Kids (MASK) Study

Denmark

Educational Outcome in Adolescence Following Pyloric Stenosis Repair Before 3 Months of Age: a Nationwide Cohort Study

Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K

Pediatric Anesthesia 2013; 23: 883-890

Methods

- This study examined the “Danish birth cohort,” which consists of those born between 1986 and 1990.
- All infants who had surgery for pyloric stenosis before the age of 3 months were compared with a randomly selected control group.
- Primary outcome: average rating subjects were given by their teachers and test average on a nationwide standardized test taken in 9th grade
- Potential confounders were identified and statistical analysis was adjusted for:
 - Gender
 - Birth weight
 - Parental ages and education level
 - Neonatal jaundice

Results/Conclusions

- In between 1986 and 1990, 779 children had pyloric stenosis repair under the age of 3 months.
- 14,665 children were in the control group.
- Those exposed to anesthesia before the age of 3 months had lower 9th grade test scores, but after multivariate analysis, there was no statistically significant difference.
- Children who had surgery for pyloric stenosis before the age of 3 months were at higher risk of having an unavailable test or teacher score.

Caveats/Limitations

- Anesthesia used in this cohort may differ from that used currently.

Netherlands Study

Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship

Bartels M, Althoff RR and Boomsma DI

Twin Research and Human Genetics 2009; 12(3): 246-253

Hypothesis

- Anesthesia administration in the first three years of life causes later learning problems.
- Children who need surgery early in life have medical problems that are associated with a vulnerability to learning disabilities.

Methods

- Data source: Young Netherlands Twin Registry
- 1,143 monozygotic twin pairs (56% female)
 - Born 1986-1995
 - Gestational age ≥ 32 weeks; birth weight ≥ 2000 grams
- Learning disability assessed at ~ 12 years
 - Educational achievement (Dutch CITO-elementary test)
 - Cognitive problems (Cognitive Problems/Inattention subscale **of the Conners' Teacher Rating Scale – Revised**)
- Twins were categorized:
 - Concordant exposed; concordant non-exposed; discordant
 - Before age 3 years and ever exposed before 12 years

Results

- Twin pairs in which one twin was exposed to anesthesia before the age of 12 and the other was not exposed to anesthesia did not have a significant difference in mean scores for education achievement or cognitive problems.
- Male twin pairs in which neither twin was exposed to anesthesia had higher educational achievement scores than twin pairs in which one or both twins were exposed to anesthesia.
- Female twin pairs in which neither twin was exposed to anesthesia had less cognitive problems than twin pairs in which one or both twins were exposed to anesthesia.
- For males exposed at any time point, their educational achievement score was lower than the educational achievement score in the concordant non-exposed group.
- And, for females, a non-significant difference in the same direction was found.

Conclusions/Recommendations

- The data provide evidence against a causal effect of anesthesia on cognitive functioning.
- The vulnerability for learning-related problems may already be present at the time the decision for surgery is made.

Caveats and Limitations

- Did not directly assess for learning disabilities instead evaluated learning-related outcomes.
- Did not assess for the specific types of anesthesia.

Mayo Clinic – Study 1

Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort

Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO

Anesthesiology 2009; 110: 796-804

Methods

- Used same database as previous studies.
- Identified children who underwent general anesthesia for any type of surgery or diagnostic procedure before their fourth birthday.
- Educational and medical records were reviewed to identify children with learning disabilities (LD).
 - Reading, written language, and math disabilities.
 - Diagnosed using three formulas involving IQ and achievement test scores.
- Cox proportional hazards regression was used.
 - Adjustments for gestational age at birth, sex, and birth weight.
- Individuals were followed from birth until age 19 years.

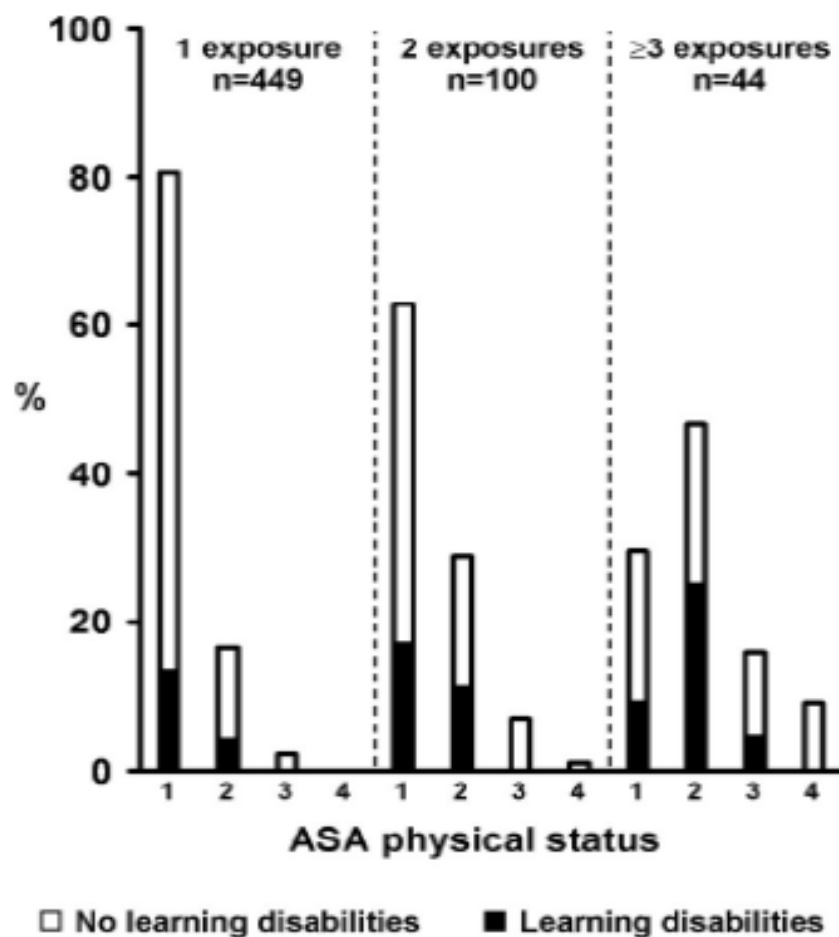
Results

- 8,548 children born during the period.
- 5,357 children included in the cohort
- 4,764 had no anesthesia exposure.
- 593 received GA before age 4 yr
 - 449 had a single anesthetic exposure
 - 100 had received two anesthetics
 - 44 had received three anesthetics

Results (continued)

- Exposed before age 4 yr, versus unexposed children
 - lower birth weight ($p < 0.001$)
 - lower gestational age ($p < 0.001$)
 - were more likely to be male ($p < 0.001$)
 - higher levels of maternal education ($p < 0.039$)
- Analysis was adjusted for first 3 differences.
- No adjustment for 4th factor; data missing for 10% of children.
- Apgar scores and peripartum complications were not different between two groups.

Results (continued)



Results

Derived from Table 6. Effects of Anesthetic Exposures before Age 4 yr on Risk for Development of Learning Disabilities

Type of Exposure	Hazard Ratio	95% Confidence Interval
Single anesthetic	1.0	0.79 – 1.27
Two anesthetics	1.59	1.06 – 2.37
Three or more anesthetics	2.60	1.60 – 4.24
Anesthetic duration \leq 30 minutes	0.93	0.56 – 1.55
Anesthetic duration \geq 120 minutes	1.65	1.19 – 2.29

Conclusions

- A single anesthetic exposure was not a risk factor for development of a LD.
- Multiple exposures were a significant risk factor.
- The data do not discern whether anesthesia contributes to LD or is a marker for other factors that do.

Caveats and Limitations

- Cannot distinguish between potential effects of anesthesia itself and other factors associated with anesthesia, e.g., stress response to surgical procedure.
- Cannot discern if children requiring surgery differ from those who do not in a way that affects risks for LD.
- Cannot exclude that requiring multiple anesthetics is a marker for conditions that increase LD risk.

Caveats/Limitations

- Children requiring repeated procedures may have a higher burden of illness, which may increase risk for LD.
- Rochester was a predominantly white, middle-class community, which limits the generalization of the results.
- It is not certain whether LD is a relevant outcome measure for assessing potential neurotoxic effects of anesthesia.

Mayo Clinic – Study 2

Cognitive and Behavioral Outcomes After Early Exposure to Anesthesia and Surgery

Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, and Warner DO

Pediatrics 2011; 128:e1053-e597

Methods

- Database used for previous studies.
- Exposed to anesthesia before two years of age (n = 350)
- Matched to 2 unexposed controls (n=700)
 - Based on risk factors for learning disabilities (LD)
 - Adjusted for co-morbidities
- Risk factors included
 - Gender
 - Mother's level of education
 - Birth weight
 - Gestational age
- Health status was quantified using
 - ASA-PS system
 - Johns Hopkins Adjusted Clinical Groups Case Mix System

Methods (continued)

- Educational records were evaluated
 - Identify children with a LD
 - Need for an individualized education program (IEP)
 - Results of tests of cognition and achievement.
- Individualized education programs were separated
 - Emotional behavioral disorders (IEP-EBD)
 - Speech and language impairments (IEP-SL)

Results

Association of Anesthetic Exposure Before Age 2 yrs With Need for Individualized Educational Programs

Individualized Educational Program Type	No. of anesthetic exposures	Hazard Ratio	95% CI
Emotional Behavioral Disorder	0	–	–
	1	0.70	0.35 – 1.42
	≥ 2	0.00 (none identified)	–
Speech and Language impairment	0	–	–
	1	1.21	0.70 – 2.10
	≥ 2	4.76	2.48-9.12

Conclusions

- Multiple exposures to anesthesia prior to age 2 years are a risk factor for deficits in learning but not behavior, even with adjustment for health status.
- Multiple anesthetic exposures were associated with learning disability and the need for an Individualized Educational Program-Speech and Language Impairment, but not for IEP-Emotional Behavioral Disorder.

Caveats/Limitations

- Subjects in this study received halothane, which is no longer in common use.
- It is impossible to distinguish between the effects of surgery and the effects of anesthesia.

Mayo Clinic- Study 3

Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia

Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanic K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT, Warner DO

Mayo Clin Proc. 2012;87(2):120-129

Methods

- Same, previously described cohort
- Subjects with ADHD identified.
- Subjects requiring general anesthesia before the age of 2 years identified.
- Health status evaluated with Johns Hopkins Adjusted Clinical Groups Case-Mix System.

Results

- 5357 subjects studied:
 - 341/5357 of these had ADHD
 - 350/5357 had general anesthesia before age 2
 - 286 had 1 anesthetic
 - 64 had ≥ 2 anesthetics
- Incidence of ADHD was $\sim 7\%$ in those who did not have anesthesia before age 2
- After adjustment for sex, birth weight, and gestational age, ≥ 2 anesthetics before the age of 2 years of age increased risk for ADHD

Conclusions

- Multiple exposures to general anesthesia prior to age 2 years increases risk for ADHD.

Caveats/Limitations

- The consequences of anesthesia and the consequences of the surgery, itself, cannot be separated.
- Those needing surgery may be different in ways important to outcomes measured.

New York State

A Retrospective Cohort Study of the Association of Anesthesia and Hernia Repair Surgery With Behavioral and Developmental Disorders in Young Children

DiMaggio C, Sun LS, Kakavouli A, Byrne MW, and Li G

J Neurosurg Anesthesiol 2009; 21: 286-291

Design

Retrospective cohort analysis

- Children born between 1999 and 2001 and enrolled in the New York State Medicaid program.
- Birth cohort of 383 children who underwent inguinal hernia repair during the first 3 years of life.
- Comparator was random sample of 5050 children.
 - Frequency-matched on age in months
 - No history of hernia-repair before age 3

Methods

- Exposure = an ICD-9 procedure code related to hernia repair
 - Inpatient or outpatient
 - Principal or secondary
 - 1999 to 2002
- Outcome = the presence of a diagnostic code for
 - Unspecified delay or behavioral disorder
 - Mental retardation
 - Autism
 - Language or speech problems
- Controlled for age, sex, and complicating birth-related conditions such as low birth weight.

Results

- Demographic characteristics of the hernia repair group and no hernia repair group differed in the following ways:
 - Male (78% hernia repair vs. 50% no hernia repair)
 - Black (29% hernia repair vs. 20% no hernia repair)
 - Potentially confounding complicating diagnoses at birth:
 - Low birth weight (<2500 g) (32% hernia repair vs. 12% no hernia repair)
 - Perinatal hypoxia (16% hernia repair vs. 1.5% no hernia repair)
 - Any secondary diagnosis
 - Gastrointestinal disorder (including hernia) (1.6% hernia repair vs. 0.1% no hernia repair)
 - CNS anomaly
- No difference between groups for
 - Age
 - Loss to follow-up

Results

Derived from TABLE 3. Cox Proportional Hazard Ratios and 95% CI for Behavioral and Developmental Disorders Associated With Hernia Repair Controlling for Age, Sex, Race, and Complicating Diagnosis at Birth, New York State Medicaid Data 1999 to 2002

Parameter	Hazard Ratio	95% CI
Anesthesia exposure	2.3	1.3 – 4.1
Age	1.0	0.9 – 1.0
Sex (male vs. female)	2.7	1.5 – 4.7
Race	1.1	1.0 – 1.1
Birth complication	1.6	1.1 – 2.5

Conclusions

- Hernia repair before 3 years of age is associated with an increased risk of subsequent diagnosis of behavioral/developmental disorders.
- The association cannot be explained by confounding due to:
 - Low birth weight
 - Comorbidity
 - Demographic characteristics

Caveats/Limitations

- Database used is a blunt instrument.
 - Unable to establish the type, route and dose of anesthetic.
 - Unable to differentiate the effects of anesthesia from those of surgery.
 - Diagnoses might be susceptible to bias resulting from misclassification, underreporting, and local practice patterns.
- Potential for bias from unmeasured cofounders, e.g., reasons for prematurity and resulting low birth weight.
- Potential for differences between children covered by Medicaid compared to other population groups.
- Long-term effects remain unknown.

New York State

Early Childhood Exposure to Anesthesia and Risk of Developmental and Behavioral Disorders in a Sibling Birth Cohort

DiMaggio C, Sun LS, Li G

Anesth Analg 2011;113:1143-51

Methods

- Retrospective
- From earlier examined cohort
- 11,648 twin-siblings in New York State Medicaid born from 1999 to 2005.
- For those children, 668 procedures were documented.
- Children diagnosed with developmental or behavioral problem before surgery were excluded.
- Compared children who had surgery under the age of 3 years with the remaining cohort.
- Also compared 138 twin-sibling pairs where one twin had surgery and the other did not.

Results

- 304 children had surgery before the age of 3 years
 - 210 had 1 surgery
 - 71 had 2 surgeries
 - 23 had ≥ 3 surgeries
- 75/304 (~25%) were given a developmental or behavioral diagnosis
- Of unexposed, 896/10,146 (~9%) were given a developmental or behavioral diagnosis
- Of the 138 twin-sibling pairs where one twin had surgery and the other did not:
 - 11 twin pairs both had a diagnosis of behavioral or developmental problem
 - 107 pairs did not have a diagnosis
 - 9 pairs in which twin who had anesthesia was given a diagnosis
 - 11 pairs in which twin who did not have anesthesia was given a diagnosis

Conclusions

- 60% increase in developmental and behavioral disorders in those who had surgery under the age of 3 years.
- More tightly matched pairwise analyses indicate that the extent to which the excess risk is causally attributable to anesthesia or mediated by unmeasured factors remains to be determined.

Caveats/Limitations

- Children born into Medicaid differ from the general population in ways that affect their health and medical care utilization

Western Australian Pregnancy Cohort –Study 1

Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia

Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, Davidson A, Wood AJJ, Li G, Sun LS

Pediatrics 2012; 130: e476- e485

Methods

- Western Australian Pregnancy Cohort has 2868 subjects born 1989 through 1992.
- This database was established to evaluate the effects of ultrasound as they are used for prenatal care.
- 260 of these subjects did not have adequate follow-up to be included in the analysis.
- Subjects were evaluated at 1, 2, 3, 5, 8, 10, 13, and 16 years-old.
- Searched for evidence of surgery before age 3 years
- Assessed the neuropsychological tests subjects had at 10 years of age

Results

- 321 had anesthesia before the age of 3 years.
- 2287 did not have anesthesia before age 3 years.
- Those who had anesthesia before age 3 years had lower scores on tests at age 10 years in areas of receptive, expressive, and total language.
- In a subgroup analysis of subjects with the most thorough follow-up information, those with single and multiple anesthetics were examined:
 - Those with a single anesthetic had deficits in abstract reasoning.
 - Those with single and multiple anesthetics had deficits in total language and receptive language.

Conclusions

- Subjects receiving anesthesia before 3 years of age had higher risk of receptive and expressive language and abstract reasoning deficits.

Caveats/Limitations

- Retrospective
- No comprehensive information on anesthesia received; no medical records.

Western Australian Pregnancy Cohort – Study 2

Comparative Analysis of Outcome Measures Used in Examining Neurodevelopmental Effects of Early Childhood Anesthesia Exposure

Ing CH, DiMaggio CJ, Malacova E, Whitehouse AJ, Hegarty MK, Feng T, Brady JE, von Ungern-Sternberg BS, Davidson AJ, Wall MM, Wood AJJ, Li G, Sun LS

Anesthesiology 2014; 120: 1319-32

Methods

- Data from Western Australian Pregnancy Cohort Study
- Extensive follow-up testing at 10 years of age
- Subgroup of 781 subjects had complete outcome data
- Examination of subjects who had anesthesia before the age of 3 years

Results

- 112/781 had an anesthetic before age 3 years.
- 669/781 did not have anesthetic before age 3 years.
- Subjects who had anesthesia before the age of 3 years had lower scores on the language portion of neuropsychological tests.
- Subjects who had anesthesia before the age of 3 years had increased diagnosis of more Behavior, Language, and Cognitive and Language and Cognitive disorders.
- Those who had anesthesia before the age of 3 did not have increased risk of “not achieving national benchmarks in academic achievement.”

Conclusions

- Anesthesia before the age of 3 years was associated with language deficit on neuropsychological tests and increase in ICD-9-coded Behavior, Language, and Cognitive disorder and ICD-9-coded Language and Cognitive disorder, but there was no difference in academic achievement tests.

Caveats/Limitations

- This study is observational.
- Do not know what anesthetic subjects received.

Clinical Investigations

- Retrospective Epidemiological Studies
 - Denmark
 - Netherlands
 - Mayo Clinic
 - New York State
 - Australia
- Prospective Epidemiological Study
 - PANDA Study
- Prospective Randomized Controlled Study
 - General Anesthesia/Spinal (GAS) Study
 - Mayo Anesthesia Safety in Kids (MASK) Study

PANDA Study

Early Childhood General Anaesthesia Exposure and Neurocognitive Development

Sun L.

British Journal of Anaesthesia 105 (S1): i61–i68 (2010)

- <http://www.kidsPANDASTudy.org>

Design/Objective

Pediatric Anesthesia and NeuroDevelopment Assessment (PANDA) Study

- Large-scale, multisite (USA), ambi-directional, sibling-matched, cohort study.
- Partially funded by FDA
- Objective: to examine the neurodevelopmental effects of exposure to general anesthesia during inguinal hernia surgery before 3 years of age.
 - Plan to enroll total 240 subjects
 - Sibling comparison group
 - Direct neuropsychological assessment

PANDA Participating Sites

- Children's Hospital of New York – Columbia University
- Boston Children's Hospital
- Children's Hospital of Philadelphia
- Chicago Children's Memorial Hospital
- Cincinnati Children's Hospital
- Vanderbilt University Children's Hospital
- Pittsburgh Children's Hospital
- University of Michigan Children's Hospital

Inclusion Criteria

- ASA PS 1 and 2
- Gestational age > 36 weeks
- Single anesthesia exposure prior to 36 months of age during inguinal hernia surgery
- Sibling within 36 months in age who had no anesthesia before 36 months of age
- Both siblings are currently between 8 years 0 months to 15 years 0 months of age

Study Progress

- 116 sibling pairs have been enrolled.

Clinical Investigations

- Retrospective Epidemiological Studies
 - Denmark
 - Netherlands
 - Mayo Clinic
 - Australia
 - New York State
- Prospective Epidemiological Study
 - PANDA Study
- Prospective Randomized Controlled Study
 - General Anesthesia/Spinal (GAS) Study
 - Mayo Anesthesia Safety in Kids (MASK) Study

GAS Study

- A Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in Infants (GAS)
- Collaborators:
 - Children's Hospital of Boston (US Sponsor)
 - Royal Children's Hospital
 - Royal Hospital for Sick Children
 - Murdoch Children's Research Institute
- www.clinicaltrials.gov Identifier: NCT00756600

GAS Study

Participating hospitals are located in:

- Australia
- Canada
- Italy
- United Kingdom
- United States

Design

- Prospective, randomized, international, observer-blinded

Treatments

- Regional Anesthesia: Bupivacaine up to 2.5 mg/kg total dose administered as single injection(s) by one of the following routes:
 - caudal or
 - subarachnoid or
 - both caudal and subarachnoid or
 - subarachnoid and ilioinguinal nerve blockade.
- General Anesthesia: Sevoflurane up to 8% for induction and maintenance. In addition, bupivacaine (up to 2.5 mg/kg) administered via caudal route or for ilioinguinal nerve block.

Study Population

Inclusion Criteria:

- Scheduled for unilateral or bilateral inguinal hernia repair
- Between 26 weeks gestational age and less than or equal to 60 weeks post-menstrual age

Study Population

Exclusion Criteria:

- Any contraindication to general or spinal/caudal anesthesia
- Pre-operative ventilation immediately prior to surgery
- Congenital heart disease that required ongoing pharmacotherapy
- Known chromosomal abnormality or any other known acquired or congenital abnormalities likely to affect development
- Children where follow-up would be difficult for geographic or social reasons
- Known neurological injury such as cystic periventricular leukomalacia (PVL), or grade 3 or 4 intra ventricular hemorrhage (ICH) (+/- post-hemorrhage ventricular dilation)
- Previous exposure to volatile anesthesia or benzodiazepines as a neonate or in the third trimester in utero.

Outcome Metrics

- Primary Outcome Measure:
Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) full scale IQ score assessed at 5 years corrected age
- Secondary Outcome Measures:
 - Bayley neurodevelopmental scale assessed at 2 years corrected age
 - Frequency and characteristics of apnea in the post- operative period

Study Progress

- 722 children have been enrolled.
- Reporting of study results:
 - For 2-year assessment: 2014
 - For 5-year assessment: 2017

Mayo Anesthesia Safety in Kids (MASK) Study

- Prospective, randomized
- Collaboration between Mayo Clinic and NCTR (FDA's National Center for Toxicological Research).
- Want to enroll 1000 children born in Rochester, MN
- Children exposed to no anesthesia, one anesthetic, or multiple anesthetics before the age of 3 years will be given NCTR operant test battery.
- NCTR operant test battery is being used to show cognitive deficits in nonhuman primates exposed to anesthesia.

Overall Summary

- Nonclinical findings
 - Mounting evidence of anesthetic-induced toxicity
 - Possible safety margins (in terms of duration) may exist
 - Possible methods to ameliorate or even prevent effects have been proposed
 - Greatest concerns: Longer durations of procedures, youngest patients, multiple procedures
- Clinical findings
 - Conflicting results for single exposures (duration frequently not considered in analysis)
 - Some clinical studies reflect findings that may correlate with concerns raised by nonclinical data.
- Causality cannot be established (surgery, anesthesia, or both).
- Prospective epidemiological study and clinical trial are underway as well as additional retrospective epidemiological studies.

Overall Summary

- Clinical issues to consider during discussions:
 - Types of additional clinical studies that will be useful
 - Design
 - Populations
 - Endpoints
 - Challenges to design of a clinical study:
 - Duration of procedure
 - Can we dissociate procedures from anesthesia?
 - Potential need for pre-op evaluation for neurocognitive functioning as well as long-term post-op follow-up and interventions

References

- Bartels,M., Althoff,R.R., and Boomsma,D.I. (2009). Anesthesia and cognitive performance in children: no evidence for a causal relationship. *Twin. Res Hum. Genet.* 12, 246-253.
- DiMaggio,C., Sun,L.S., Kakavouli,A., Byrne,M.W., and Li,G. (2009). A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. *J Neurosurg. Anesthesiol.* 21, 286-291.
- DiMaggio,C., Sun,L.S., and Li,G. (2011). Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. *Anesth. Analg.* 113, 1143-1151.
- Flick,R.P., Katusic,S.K., Colligan,R.C., Wilder,R.T., Voigt,R.G., Olson,M.D., Sprung,J., Weaver,A.L., Schroeder,D.R., and Warner,D.O. (2011). Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* 128, e1053-e1061.
- Flick,R.P., Nemergut,M.E., Christensen,K., and Hansen,T.G. (2014). Anesthetic-related neurotoxicity in the young and outcome measures: the devil is in the details. *Anesthesiology.* 120, 1303-1305.
- Hansen,T.G., Pedersen,J.K., Henneberg,S.W., Morton,N.S., and Christensen,K. (2013). Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study. *Paediatr. Anaesth* 23, 883-890.
- Ing,C., DiMaggio,C., Whitehouse,A., Hegarty,M.K., Brady,J., von Ungern-Sternberg,B.S., Davidson,A., Wood,A.J., Li,G., and Sun,L.S. (2012). Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 130, e476-e485.
- Ing,C.H., DiMaggio,C.J., Malacova,E., Whitehouse,A.J., Hegarty,M.K., Feng,T., Brady,J.E., von Ungern-Sternberg,B.S., Davidson,A.J., Wall,M.M., Wood,A.J., Li,G., and Sun,L.S. (2014). Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. *Anesthesiology.* 120, 1319-1332.
- Sprung,J., Flick,R.P., Katusic,S.K., Colligan,R.C., Barbaresi,W.J., Bojanic,K., Welch,T.L., Olson,M.D., Hanson,A.C., Schroeder,D.R., Wilder,R.T., and Warner,D.O. (2012). Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. *Mayo. Clin Proc.* 87, 120-129.
- Wilder,R.T., Flick,R.P., Sprung,J., Katusic,S.K., Barbaresi,W.J., Mickelson,C., Gleich,S.J., Schroeder,D.R., Weaver,A.L., and Warner,D.O. (2009). Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology.* 110, 796-804.